NIH Office of AIDS Research (OAR) Meeting on Restructuring NIH-Sponsored AIDS Clinical Trials Networks
May 19, 2004

Focus: Development of "Guiding Principles" for DAIDS RFA FY '06 Draft Concept for DAIDS consideration.

OAR Guiding Principles:

Principle 1: The highest priority science must drive the structure of NIAID's clinical trials endeavor, rather than vice-versa. The structure/mechanism of how NIAID's resources are used for clinical research must be flexible and serve the scientific priorities. The Working Group feels that one mechanism will be unable to accomplish the breadth of the clinical research that needs to be conducted. For example, laboratory-based clinical translational research of short or moderate duration may be optimally conducted in the context of a standing network funded to conduct multiple similar research projects. However, operational research projects that require very large numbers of patients and/or long-term follow-up
(i.e., operational/treatment strategy research or vaccine effectiveness studies) may be optimally conducted as a single study investigator-initiated project or as a coordinating center grant. Alternatively, operational research on scaling-up ART as part of primary health care delivery in resource poor settings (Africa, Asia,
South America, the Caribbean, etc.) may require development of dispersed rural research sites as a network coordinated by an urban center, rather than the urban site *per se*. The integration of HIV prevention (biologic as well as socio-behavioral) and treatment is a key public health and scientific priority. Thus, structural linkages between programs of research on prevention interventions and optimizing HIV treatments with programs for delivery of prevention interventions and treatment may be necessary. Scientific leadership, decision-making, and initiation of research ideas are best placed in the hands of those actually conducting the clinical research and, as such, clinical research structures should be established to support this principle. As scientific priorities may shift, research support mechanisms must be flexible enough to incorporate new ideas and new investigators to address the science. DAIDS must support a variety of types of clinical research structures in order to address the highest priority science.

Principle 2: DAIDS scientific priorities for AIDS clinical research in the areas of therapeutics, vaccines, and prevention should be more clearly defined now, be integrated with and reflect the priorities and plans of other NIH HIV/AIDS research endeavors, and be reassessed annually. The annual NIH Plan for HIV-Related Research should be used as a guide to develop these specific priority questions along with regular communication between NIAID and the other NIH Institutes, Centers and Divisions that support HIV/AIDS clinical research. The ARAC should assist DAIDS in elaborating and prioritizing these questions and ARAC is encouraged to convene specific meetings with expert ad hoc members (national or international), as needed. These scientific priorities should then inform the structure of DAIDS' clinical trials endeavors.

Principle 3a: Objective external review of major clinical trials should be routine. The major clinical trials to be conducted by the networks should undergo objective external review – perhaps by standing advisory committees, such as the AIDS Vaccine Research Working Group or by ARAC, supplemented by appropriate ad hoc national or international experts.

Principle 3b: Regular external evaluation of the progress of the standing networks should be conducted and that oversight should be integrated into network operations. The ARAC is the logical group to conduct network evaluations. Supplementing ARAC with clinical trials experts, and experts in operations or effectiveness research would be appropriate as needed.

Principle 4: Community involvement and participation must be routinely incorporated into all components of DAIDS-supported clinical research and supported through specific mechanisms with investment of resources (for education, technical assistance, and to ensure meaningful involvement, etc.). An evaluation of the effectiveness of community involvement should also be integrated into all DAIDS-supported clinical research activities.

Principle 5: Protocol development and implementation must be streamlined and be appropriate for the science being conducted. Streamlined protocol development and implementation should minimize DAIDS staff (or contractor) involvement. Serious consideration should be given to establishment of interdisciplinary project management teams for each project that would be provided sufficient resources and fixed deadlines to develop and implement each stage of new product or intervention evaluation.

Principle 6: To provide better coordination and efficiency and avoid redundancy, strong incentives should be given for intra-country communications and collaboration between all similar resources (i.e., reference labs, research support contracts, community input, etc. supported by NIH [all Institutes, Centers and Divisions], but also by CDC, EU/EDCTP, ANRS, MRC, WHO, philanthropy, etc.). Promotion of local or in-country scientific and administrative leadership, ownership and investment in the research enterprise could also promote improved coordination and efficiency.

Principle 7a: Duplication of network core resources should be minimized wherever possible by use of common resources. For example, common data management, operations, and administrative support functions should be considered/used if DAIDS funds more than one clinical research network to conduct multiple trials. In order to retain the flexibility needed to best address scientific priorities (for example the conduct of trials with very large numbers of patients,
i.e., sample size of thousands, and/or long-term follow-up, i.e., for 5, 10 years or more), will likely need independent research resources distinct from those of standing research networks.

Principle 7b: Avoidance of redundancy in network missions is desirable. Existing or potential overlap in network missions can lead to confusion, competition for precious resources, and inefficiency. For example, redundancy in network mission could allow international or domestic network sites to submit or participate in similar protocols through multiple networks sequentially or even simultaneously. Coordination and communication among trials leadership, including statistical leadership, will be required to minimize redundancy.

Principle 8: Training and capacity building that promotes local or in-country ownership/investment in the research enterprise must accompany research support for sites in both U.S. and international resource-poor settings. DAIDS supported clinical research in resource poor settings (domestic or international) must catalyze linkages that will foster training and capacity building perhaps in part through linkages to CIPRA, CFAR, AITRP, ICOHRTA, perhaps with network support for junior investigators trained by CIPRA, CFAR, and Fogarty International Center programs. In addition, non-NIH linkages should be sought with other sources for training and capacity building such as governmental agencies, foundations, and other health organizations. All research proposals conducted in resource poor settings must contain a clear and convincing training and capacity building component in order to be eligible for NIAID funds.

Principle 9: DAIDS clinical research funding should support appropriate levels of infrastructure and provide DAIDS-controlled incentives to support the direct costs for the conduct of clinical trials. Funding of fixed costs for central and clinical site infrastructure should be balanced with funding for incremental and variable costs required for the conduct of a specific clinical trial. In this way, clinical research funds are held in reserve to support the major trials approved by a review committee. The goals are to "incentivize" timely conduct of essential research and to retain sufficient funds in reserve to actually fund the research. For example, a portion of DAIDS' total $400M for clinical trials – perhaps a third – could be committed to sustaining and building infrastructure, while the remainder could be allocated <u>across</u> networks, to fund approved trials, as well as the additional infrastructure needed to conduct these trials.